

Combination gene therapy treats multiple age-related diseases

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As we age, our bodies tend to develop diseases like heart failure, kidney failure, diabetes, and obesity, and the presence of any one disease increases the risk of developing others. Traditional drug development targets only one condition per drug, largely ignoring the interconnectedness of age-related diseases and requiring patients to take multiple drugs, which increases the risk of negative side effects.

A new study from the Wyss Institute for Biologically Inspired Engineering at Harvard University and Harvard Medical School (HMS) reports that a single administration of an adeno-associated virus (AAV)-based gene [therapy](#) delivering combinations of three longevity-associated [genes](#) to [mice](#) dramatically improved or completely reversed multiple [age-related diseases](#), suggesting that a systems-level approach to treating such diseases could improve overall health and lifespan. The research is reported in *PNAS*.

"The results we saw were stunning, and suggest that holistically addressing aging via gene therapy could be more effective than the piecemeal approach that currently exists," said first author Noah Davidson, Ph.D., a former Research Scientist at the Wyss Institute and HMS who is now the Chief Technology Officer of Rejuvenate Bio. "Everyone wants to stay as healthy as possible for as long as possible, and this study is a first step toward reducing the suffering caused by debilitating diseases."

The study was conducted in the lab of Wyss Core Faculty member George Church, Ph.D. as part of Davidson's postdoctoral research into the genetics of aging. Davidson, Church, and their co-authors honed in on three genes that had previously been shown to confer increased health

and lifespan benefits in mice that were genetically engineered to overexpress them: FGF21, sTGF β R2, and α Klotho. They hypothesized that providing extra copies of those genes to non-engineered mice via gene therapy would similarly combat age-related diseases and confer health benefits.

The team created separate gene therapy constructs for each gene using the AAV8 serotype as a delivery vehicle, and injected them into mouse models of obesity, type II diabetes, heart failure, and renal failure both individually and in combination with the other genes to see if there was a synergistic beneficial effect.

FGF21 alone caused complete reversal of weight gain and type II diabetes in obese, diabetic mice following a single [gene therapy](#) administration, and its combination with sTGF β R2 reduced kidney atrophy by 75% in mice with renal fibrosis. Heart function in mice with [heart failure](#) improved by 58% when they were given sTGF β R2 alone or in combination with either of the other two genes, showing that a combined therapeutic treatment of FGF21 and sTGF β R2 could successfully treat all four age-related conditions, therefore improving health and survival. Administering all three genes together resulted in slightly worse outcomes, likely from an adverse interaction between FGF21 and α Klotho, which remains to be studied.

Importantly, the injected genes remained separate from the animals' native genomes, did not modify their natural DNA, and could not be passed to [future generations](#) or between living animals.

"Achieving these results in non-transgenic mice is a major step toward being able to develop this treatment into a therapy, and co-administering multiple [disease](#)-addressing genes could help alleviate the immune issues that could arise from the alternative of delivering multiple, separate gene therapies for each disease," said Church, who is also a Professor of

Genetics at HMS and Professor of Health Sciences and Technology at Harvard and MIT. "This research marks a milestone in being able to effectively treat the many diseases associated with aging, and perhaps could lead to a means of addressing aging itself."

More information: Noah Davidsohn et al., "A single combination gene therapy treats multiple age-related diseases," *PNAS* (2019).

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